Analysis and comment

Research protocols

Waiving confidentiality for the greater good

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Research protocols are usually kept confidential to protect intellectual and commercial interests. But secrecy can also hide deviations that affect the validity of results and threaten the integrity of medical research

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Recent high profile events have highlighted the harms of undisclosed research data,[1 2] and methodological studies have found important discrepancies between the protocols and publications of randomised trials.[3–5] These findings have undermined the credibility of clinical research. Comparisons between the protocol and the published study constitute the most reliable means of evaluating the conduct and reporting of research. However, accessing the confidential protocols and amendments approved by research ethics committees is difficult. Formal policies do not exist for granting access to these documents without requiring permission from researchers or sponsors, and standards vary widely across individual committees within and between countries. We outline the controversies and propose a procedural framework for allowing external reviewers access to trial protocols for methodological research and oversight.

Role of ethics committees

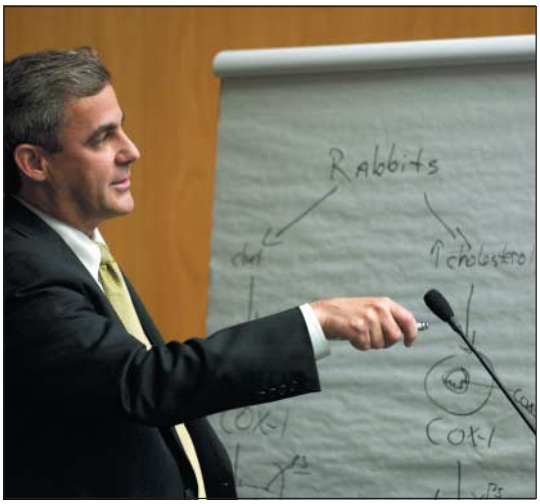
Ethics review is under assault in many countries as being needlessly bureaucratic, subject to inexplicable variation, and of uncertain value.[6 7] Although research ethics committees are responsible for ensuring that trials are reported and carried out as they have been approved,[8–10 w1] most committees are not required to do more than request interval reports from researchers.[11 12]

Comparing publications with the original protocols and amendments is an objective means of evaluating reporting of trials and adherence to the protocol. Discrepancies may indicate that the study was not performed as originally intended; subject to amendments that were not officially submitted to ethics committee for approval; or misrepresented in the publication. This oversight mechanism has become increasingly recognised by some journals, which now require authors to submit the trial protocol with the manuscripts as well as trial registration.[w2-w4]

Importance of access to protocols

Access to protocols by stakeholders during and after the trial is important for several reasons (table 1). After the trial is complete, comparisons of publications with protocols and amendments are crucial to monitoring for accurate and complete reporting. Protocols and submitted amendments constitute the only objective description of what was planned for a study. Other sources of information can be tainted by an awareness of the study results or the accuracy of their reporting in publications. Any substantive deviations from the approved protocol should be reported to the ethics committee[13–16] and described in resulting publications.[17] By defining outcomes and analysis plans before data collection, protocols protect against potentially biased analyses and subsequent selective reporting. However, protocols are not usually available in the public domain.

At present, publications are the main publicly available source of information about a trial's conduct and results. These reports should reflect the original protocol and substantive amendments, as readers must be fully informed to judge the potential for bias. Unfortunately, important unacknowledged deviations are



MARY GODLESKI/AP/EMPICS

Scientist Briggs Morrison tells jurors that Merck & Co conducted key studies of Vioxx before putting it on the market

References w1-w12 and a sample confidentiality agreement are on bmj.com

common, even for elements as crucial as the definition of primary outcomes.[3 4] Failure to report such amendments can mislead readers and constitutes a breach of standards of scientific conduct.[w5]

Debate over access to protocols

The interests of everyone affected by the research must be balanced during the sensitive process of identifying protocol deviations (table 2). The key issue is whether trialists or sponsors need to give permission to those accessing their protocols. When applications are made to an ethics committee or funding agency, there is an understanding that the submitted information will remain confidential. This understanding is primarily a professional courtesy with the actual ethical, legal, and regulatory requirements varying across countries. Most committees require their members to sign confidentiality agreements, which is understandable in an era where the protection of commercial or intellectual interests can help to maintain a competitive advantage.

However, it should be possible to ensure that submitted information remains confidential while enabling external reviewers to examine the files without explicit permission from applicants. Furthermore, although safeguards should be established to minimise potential threats to competitive interests, the accurate dissemination of knowledge should take precedence in order to fulfil ethical obligations to study participants and future patients.

A permission waiver for accessing trial protocols and amendments through ethics committees or funding agencies can be justified on several principles (box). These principles have also been used to justify consent waivers when accessing personal health information for epidemiological studies.[12 16 18–20]

Societal benefit

Assessment of protocol deviations has direct societal importance because it enhances the reliability of healthcare evidence. It also fulfils the obligations of ethics committees and funding agencies to ensure that trials are conducted and reported in a manner consistent with the approved protocol. Of greatest importance is the ethical obligation to trial participants, who take on a degree of risk in exchange for their contributions to accurately reported scientific knowledge. Precedent has been set for conducting extensive protocol reviews when justified by a greater good,[w6] and policy statements have affirmed the role of ethics committees in allowing "periodic review by a third party of the documents generated by [a] study."[12]

Conditions for waiving permission to access trial protocols

- Societal benefit outweighs the consequences of the waived confidentiality
- Minimal risk—waiver is unlikely to adversely affect the rights and welfare of trialists and sponsors
- The methodological research and oversight could not practicably be carried out without the permission waiver

Table 1 Benefits of access to trial protocols: who, when, and why

Who	When	Why
Study participants	Before enrolment	Informed consent
Research ethics committees	Before enrolment	Ethical review and oversight from trial inception through to reporting
Funding agencies	Before enrolment	Scientific review and oversight from trial inception through to reporting
Systematic reviewers	After trial inception	Awareness of ongoing, unpublished, and published studies; oversight of accurate trial reporting in publications; detailed quality assessment
External reviewers	After trial inception	Monitoring of ongoing trials and dissemination of results; oversight of accurate reporting in publications; detailed quality assessment
Journal editors and peer reviewers	Before publication	Oversight of accurate reporting in submitted publications; detailed quality assessment
Health regulatory agencies	Before regulatory approval	Oversight of accurate reporting of submitted trial data; detailed quality assessment

Minimal risk

Although trialists and sponsors often raise concerns about protecting their competitive advantage, the risks of a permission waiver can be minimised by limiting disclosure to those directly reviewing the protocol. Trial participants would not be harmed, and would in fact benefit from knowing that the reported study corresponds closely to that which was originally approved for their participation.

Scientific rigour and feasibility

The main scientific concern is the bias introduced by the permission seeking process. Sponsors and researchers with substandard reporting practices would be less likely to allow additional scrutiny. The requirement for permission would thus undermine the validity of the protocol review process because of inevitable response bias.

Furthermore, without access to protocol information, identifying a representative cohort of randomised trials would be cumbersome and unproductive. Investigators for every approved clinical study would have to be contacted, even though many studies will not be randomised trials. Contact details will also have changed, and response rates to surveys are often suboptimal.[8 w7-w9]

Table 2 Potential opposing interests of parties affected by access to trial protocols

	Supporting access	Opposing access
Trial investigators	Ensuring high quality research	Protecting intellectual secrets
Commercial sponsors	Ensuring high quality research	Protecting intellectual and commercial secrets
Non-commercial sponsors	Ensuring unbiased, high quality research, as originally approved	
	Ensuring transparent, accurate reporting of methods and results	
Research ethics committees	Ensuring unbiased, high quality ethical research that is consistent with approved protocol	Minimising administrative burden of retrieving archived documents
	Ensuring transparent, accurate reporting of methods and results	
Study participants	Expecting transparent, high quality conduct and accurate, public reporting of studies in which they voluntarily participated	
Public (especially future patients)	Expecting transparent, high quality conduct and accurate, public reporting of research to guide health care	
Journals, peer reviewers, and readership	Ensuring transparent, accurate reporting of methods and results	
Governments	Ensuring reliable research data for policy making	

Finally, although the quality of protocols is heterogeneous, they are the best source of information for evaluating the accuracy of trial reporting. Self reported data from investigators or sponsors have been shown to be unreliable.[3 4] Although prospective trial registration will ensure that some information is publicly available,[21 w4] current registers rely primarily on voluntary submissions and are generally far less comprehensive than protocols.

Experiences with accessing trial protocols

Accessing information held by ethics committee can be difficult, even when it is stated to be in the public domain.[22] For methodological research, several of us (AWC, DGA, DG, JAS, FC) approached committees in various countries to request retrospective access to approved study protocols without explicit permission from trialists and sponsors. The responses varied.

We were denied permission by committees in the United Kingdom (2001-2), Australia (2003), and South Africa (2005). The committee at a Canadian university approved our study but then terminated it prematurely on the advice of university lawyers. Several committees said that they could not even release the names or contact details of investigators and sponsors.

In contrast, we received favourable responses from committees in Denmark (2002) and France (1998), as well as the federal research funding agency in Canada (Canadian Institutes of Health Research, 2002). Each project was adopted as a joint venture between the institution and the reviewers. We signed confidentiality agreements and were given unrestricted access to protocols.

Procedural framework for granting access to trial protocols

Our variable experiences highlight the need for formal policies to handle external requests for permission waivers when accessing confidential protocols as part of a methodological study. Appropriate governance is required to balance the need for research oversight with the need for safeguards to protect the interests of trialists and sponsors. Little research has been published on procedures for obtaining access to study protocols. We know of seven reviews that compared confidential protocols to publications using five independent cohorts,[3 4 w10-w14] one of which required permission from individual researchers.[w13]

One mechanism is to allow independent reviewers to examine protocols in collaboration with ethics committees or funding agencies. Such a review would identify areas for improvement in the reporting of trials as well as the quality of protocols. This would also enable some under-resourced committees to fulfil their monitoring obligations through externally funded researchers, who would be required to sign a confidentiality agreement.

Another potential mechanism would be to create an independent and public privacy board, separate from the ethics committee, with statutory force to provide access to protocols and amendments. Such a body, akin to the privacy boards introduced in the United States and France,[23 24] could be staffed by people with expertise in ethics, public health, and the laws of privacy, contract, and intellectual property. It could be empowered to authorise access to research protocols with a permission waiver if, among other considerations, it is satisfied that the independent reviewer is requesting access for the sole purpose of reviewing protocols to serve a greater public good and undertakes in writing to protect the privacy and proprietary interests of those concerned (see bmj.com for a sample agreement). National or international regulation would be needed to standardise the composition and policies of these boards.

As with health services research, additional safeguards should always be applied to ensure confidentiality when accessing protocols. Reviewers should be required to observe standards enshrined in codes of ethics for professionals. Although ethics committees and funding agencies have a right to know which trials showed serious problems, published reviews should provide only aggregate data to preserve the anonymity of individual studies. Violations of confidentiality provisions should be interpreted as serious breaches of professional practice. Finally, at the time of submission of protocols, committees should state explicitly that applications may be audited in the future.

Summary points

- Comparing research protocols with subsequent publications helps to ensure accurate dissemination of trial methods and results
- This fulfils ethical obligations to participants and protects future patients
- Many ethics committees do not allow external reviewers access to trial protocols for methodological research without permission from protocol authors and sponsors
- The societal benefits of access outweigh the confidentiality rights of researchers and commercial funders
- A formal framework is needed for granting access to approved protocols without permission from individual trialists

Conclusions

The arguments for granting external reviewers permission waivers to access confidential research protocols are compelling. As more methodological research is conducted, the justification for comprehensive access to protocols should become widely accepted. It should also prompt institutions to support this type of research as a joint venture to monitor studies that they approve and identify those that remain unpublished. Requiring registration of protocol information as a condition of approval will further enhance transparency.[21] Although our discussion has been limited to randomised trials, similar arguments could be applied to other study designs. Ultimately the

integrity of medical research must be of top priority to protect study participants and future patients. This principle outweighs concerns over confidentiality, provided that safeguards are established to minimise threats to the competitive interests of investigators and sponsors.

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Diagnosis

Comparative accuracy: assessing new tests against existing diagnostic pathways

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Most studies of diagnostic accuracy only compare a test with the reference standard. Is this helpful?

Evaluating diagnostic accuracy is an essential step in the evaluation of medical tests.[1 2] Yet unlike randomised trials of interventions, which have a control arm, most studies of diagnostic accuracy do not compare the new test with existing tests.

We propose a modified approach to test evaluation, in which the accuracy of new tests is compared with that of existing tests or testing pathways. We argue that knowledge of other features of the new test, such as its availability and invasiveness, can help define how it is likely to be used, and we define three roles of a new test: replacement, triage, and add-on (fig 1).

Knowing the future role of new tests can help in designing studies, in making such studies more efficient, in identifying the best measure of change in accuracy, and in understanding and interpreting the results of studies.

Replacement

New tests may differ from existing ones in various ways (table 1). They may be more accurate, less invasive, easier to do, less risky, less uncomfortable for patients, quicker to yield results, technically less challenging, or more easily interpreted.

For example, biomarkers for prostate cancer have recently been proposed as a more accurate replacement for prostate specific antigen. A rapid blood test that detects individual activated effector T cells (SPOT-TB) has been introduced as a better way to diagnose tuberculosis than the tuberculin skin test. Myelography has been replaced in most centres by magnetic resonance imaging to detect spinal cord injuries, not only because it provides detailed images, but also because it is simpler, safer, and does not require exposure to radiation (table 2).

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